

Induction Therapy for Locally Advanced, Resectable Esophagogastric Cancer

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Abstract

© 2017 Wolters Kluwer Health, Inc. Preoperative chemotherapy and radiation for localized esophageal cancer produces cure rates near 30% when combined with surgical resection. Vandetanib, a small molecule receptor tyrosine kinase inhibitor of VEGFR-2, VEGFR-3, RET, and EGFR, demonstrated synergy with radiation and chemotherapy in preclinical models. We conducted a phase I study to assess the safety and tolerability of vandetanib when combined with preoperative chemoradiation in patients with localized esophageal carcinoma who were surgical candidates. Methods: Patients with stage II-III esophageal and gastroesophageal junction carcinoma without prior therapy were enrolled in a 3+3 phase I design. Patients received once-daily vandetanib (planned dosing levels of 100, 200, and 300 mg) with concomitant daily radiotherapy (1.8 Gy/d, 45 Gy total) and chemotherapy, consisting of infusional 5-FU (225 mg/m²/d over 96 h, weekly), paclitaxel (50 mg/m², days 1, 8, 15, 22, 29) and carboplatin (AUC of 5, days 1, 29). Results: A total 9 patients were enrolled with 8 having either distal esophageal or gastroesophageal junction carcinomas. All patients completed the planned preoperative chemoradiation and underwent esophagectomy. Nausea (44%) and anorexia (44%) were the most common acute toxicities of any grade. One grade 4 nonhematologic toxicity was observed (gastrobronchial fistula). One additional patient suffered a late complication, a fatal aortoenteric hemorrhage, not definitively related to the investigational regimen. Five (56%) patients achieved a pathologic complete response. Three (33%) additional patients had only microscopic residual disease. Five (56%) patients remain alive and disease free with a median follow-up of 3.7 years and median overall survival of 3.2 years. The maximum tolerated dose was vandetanib 100 mg/d. Conclusions: Vandetanib at 100 mg daily is tolerable in combination with preoperative chemotherapy (5-FU, paclitaxel, carboplatin) and radiation therapy with encouraging efficacy worthy of future study.

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Keywords

5-fluorouracil, carboplatin, esophageal cancer, paclitaxel, radiotherapy, surgery, vandetanib

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